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February 21, 2008

PATENT APPLICATION
Attorney's Docket No.: 3632.0001-000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentees: Klaus Sommermeyer, Franz Cech, Burghard Weidler, and Klaus Henning

Patent No: 5,218,108

Issued: June 8, 1993

For: HYDROXYLETHYLSTARCH (HES) AS PLASMA EXPANDER AND PROCESS FOR PREPARING HES

Date: 2/21/08 Express Mail Label No. EV214912970 US

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

MAIL STOP HATCH-WAXMAN PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an application for extension of patent term under 35 U.S.C. § 156 and 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.770 and 1.775 for U.S. Patent 5,218,108 ("the '108 Patent").

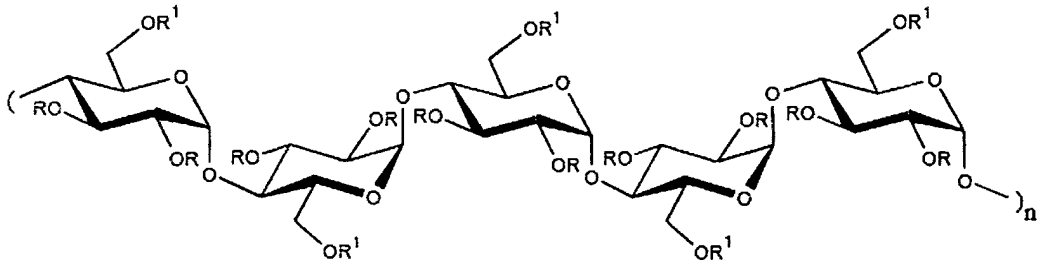
There is one owner of interest in the '108 Patent: Fresenius Kabi (referred to as the "Owner"). Copies of United States Patent and Trademark Office ("US PTO") records as well as additional documents confirming that title resides in the Owner is attached as Exhibit A.

Owner, through the undersigned, represent that it is the owners of record of the '108 Patent and hereby request an extension of the patent term.

The remainder of the sections of this application correspond with subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a).

§1.740(a)(1): *A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.*

The following information is set forth in the package insert or product insert for the approved product. A copy of the Package Insert is included herein as Exhibit B. The brand name of the approved product is VOLUVEN®. The active ingredient of VOLUVEN® is 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection. Hydroxyethyl starch in VOLUVEN® is a synthetic colloid for use in plasma volume replacement. Hydroxyethyl starch is a derivative of thin boiling waxy corn starch, which mainly consists of a glucose polymer (amylopectin) predominately composed of α-1-4-connected glucose units with several α-1-6-branches. Substitution of hydroxyethyl groups on the glucose units of the polymer reduces the normal degradation of amylopectin by α-amylase in the body. The chemical name of the class of hydroxyethyl starch is poly(O-2—hydroxyethyl) starch. The notation "130" in the active ingredient of VOLUVEN® indicates the mean molecular weight of the active ingredient, and specifically indicated that the mean molecular weight is 130,000 Daltons, with a range of 110,000 - 150,000 Daltons. The notation "0.4" indicates a low molar substitution by hydroxyethyl groups of 0.4 (with a range from 0.38 - 0.45) on glucose units of the starch. The low molar substitution (0.4) is the main pharmacological determinant for the beneficial effects of Voluven® on pharmacokinetics, intravascular volume and hemodilution. The pattern of hydroxyethyl substitution (C_2/C_6 ratio) is approximately 9:1. The concentration is 6%. The structural formula of hydroxyethyl starch is, as depicted on the package insert, as follows:



R = -H, $-CH_2CH_2OH$
R^1 = -H, $-CH_2CH_2OH$ or glucose units

§1.740(a)(2): *A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.*

Regulatory review occurred under Section 505(i) and 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (Title 21, United States Code Sections 355(i) and 355(b)(2)).

§1.740(a)(3): *An identification of date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.*

VOLUVEN® received approval in a letter dated December 27, 2007. A copy of the approval letter is attached as Exhibit C.

§1.740(a)(4): *In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.*

The sole active ingredient in VOLUVEN® is, as stated above, 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection. No product has been previously approved for commercial marketing or use under the Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act containing this active ingredient alone or in combination. This active ingredient differs from the active ingredients of other hydroxyethyl starch compositions currently available. For example, it is noted that a product Hextend®, containing a high molecular weight hetastarch having high molar substitution, was approved under NDA 20-0952 on March 31, 1999. According to the package insert for Hextend®, the hetastarch component of Hextend® is the same as in the approved Hetastarch Injection products (6% Hetastarch in 0.9% Sodium Chloride Injection). The mean molecular weight of the hetastarch of Hextend® is 670,000 Daltons with a range of 450,000 Daltons to 800,000 Daltons, and the molar substitution of the hetastarch of Hextend® is 0.75. The hydroxyethyl starch of Hextend® thus is

6% hydroxyethyl starch 670/0.75. Because the molecular weights differ so significantly and the molar substitutions also differ, and because of other factors such as branching, the active ingredient of VOLUVEN® differs from the active ingredient of the Hextend® product.

§1.740(a)(5): *A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.740(f) and an identification of the date of the last day on which the application could be submitted.*

This application is being submitted within the sixty day period following the approval of the VOLUVEN® NDA on December 27, 2007 We believe that the last day on which this submission can be made is February 25, 2008.

§1.740(a)(6): *A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.*

U.S. Patent 5,218,108
Inventors: Klaus Sommermeyer, Franz Cech, Burghard Weidler, and Klaus Henning
Issued: June 8, 1993
Filed: June 5, 1990
Date of Expiration: June 8, 2010

§1.740(a)(7): *A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.*

A copy of U.S. Patent 5,218,108, including the entire specification, claims, and drawings, is attached as Exhibit D.

§1.740(a)(8): *A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.*

No disclaimer or reexamination certificate has been issued for the '108 Patent. The first maintenance fee was paid on November 25, 1996; the second maintenance fee was paid on

November 13, 2000, and the third maintenance fee was paid on November 24, 2004. A copy of the USPTO maintenance fee record for this patent is attached as Exhibit E.

§1.740(a)(9): *A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: (i) The approved product, if the listed claims include any claim to the approved product; (ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and (iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.*

Claims 1-7 of the '108 Patent are directed to pharmaceutical compositions comprising hydroxyethyl starch. The following chart shows how applicable patent Claims 1 and 2 read on Fresenius' approved product:

Claim	**Product**
1. Hydroxyethyl starch for use as plasma expander obtainable by hydrolytic pre-degradation of a starch rich in amylopectin, partial hydroxyethylation up to a certain substitution degree in the presence of alkali and subsequent hydrolytic degradation to a certain molecular weight, characterized in that	The approved product contains hydroxyethyl starch for use as a plasma expander, prepared by pre-degrading starch rich in amylopectin, followed by etherification which results in partial hydroxyethylation, and by subsequent hydrolytic degradation.
it has a mean molecular weight of 60,000-600,000 and a substitution degree MS of 0.15 to 0.5,	The approved product has a mean molecular weight within this range, and a substitution degree MS within this range.
the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and	The approved product has such a ratio within this range.
the substitution degree DS lies in the range from 0.15 to 0.5.	The approved product has a substitution degree DS within this range.

2. Hydroxyethyl starch according to claim 1, characterized in that it has a mean molecular weight of 80,000 to 400,000 and a substitution degree MS of 0.2-0.4, the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.15 to 0.40.	The approved product has these characteristics.

§1.740(a)(10): *A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:*

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued.

(A) Fresenius Kabi filed an Investigational New Drug (IND) application, BB-IND 9740,) for hydroxyethyl starch on March 23, 2001, and the FDA indicated that it was received on March 26, 2001, in a letter dated April 5, 2001. A copy of this letter is attached as Exhibit F. The IND has an effective date 30 days after the receipt of the IND, which is April 24, 2001.

(B) Fresenius Kabi submitted a New Drug Application (NDA) on February 28, 2007, under BN070012.

(C) The NDA was approved on December 27, 2007, under the existing NDA BN070012 to Fresenius Kabi (Exhibit C).

§1.740(a)(11): *A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.*

Attached as Exhibit G is a chronology briefly describing the significant activities and dates with respect to Fresenius' efforts to seek approval of VOLUVEN®.

§1.740(a)(12): *A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.*

Applicant believes that the '108 Patent is eligible for an extension pursuant to 35 U.S.C. 156(a) and the applicable provisions of 37 C.F.R. 1.710 *et seq.* Using calculations made in accordance with 37 C.F.R. 1.775, the '108 Patent is entitled to a term extension of 1,371 days (the "Term Extension Period"). The Term Extension Period was determined as follows:

Length of Regulatory Review Period

Under section 1.775(c), the length of the regulatory review period is 2,439 days, representing the sum of (1) the number of days in the period beginning on the effective date of the IND (April 24, 2001) and ending on the day before the Submission Date of the NDA (February 27, 2007) (2,136 days) and (2) the number of days in the period beginning on the Submission Date of the NDA (February 28, 2007) and ending on the date that the Product's NDA was approved (December 27, 2007) (303 days).

Length of Patent Term Extension

Under 1.775(d), a total of 1,068 days were subtracted from the 2,439 day length of the Regulatory Review Period, as follows:

(i) 0 days were prior to the date on which the '108 Patent issued;

(ii) 0 days during which the applicant did not act with due diligence; and

(iii) 1,068 days representing one-half the number of days (2,136 days) remaining in the period defined by paragraph (c)(1) after which a total of 0 days were subtracted in accordance with paragraphs (d)(1)(i) and (d)(1)(ii).

Thus, the period calculated under section 1.775(d)(1) is 1,371 days.

The period calculated under section 1.775(d)(2), by adding 1,371 days to the original expiration date of the '108 patent (July 8, 2010), ends on April 9, 2014.

The period calculated under section 1.775(d)(3), by adding 14 years to the date of approval of the application under section 505 of the Federal Food Drug and Cosmetics Act, ends on December 27, 2021.

The date selected under section 1.775(d)(4), by comparing the two dates and selecting the earlier, is April 9, 2014.

Because the '108 Patent issued after September 24, 1984, the date determined under section 1.775(d)(5) is arrived at by adding 5 years to the original expiration date of the '108 Patent (July 8, 2015), and comparing that date (July 8, 2015) to the date determined under section 1.775(d)(4), results in selection of April 9, 2014 as the earlier date and thus the date to which the term of the '108 Patent should be extended.

§1.740(a)(13): *A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.*

Applicant, through the undersigned representative, hereby acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

§1.740(a)(14): *The prescribed fee for receiving and acting upon the application for extension.*

The prescribed fee for receiving and acting upon this application is $1,120.00. A check in this amount is submitted with this application. Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to Deposit Account No. 08-0380. A copy of this letter is enclosed for accounting purposes.

§1.740(a)(15): *The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.*

Please direct all inquiries and correspondence relating to this application for patent term extension to:

Brian T. Moriarty, Esq.
Elizabeth W. Mata, Esq.
Customer No.: 021005
Hamilton, Brook, Smith & Reynolds, P.C.
530 Virginia Road
P.O. Box 9133
Concord, MA 01742
Tel: (978) 341-0036

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

Steven G. Davis for Elizabeth W. Mata

By _____ Registration No. 39,652

Elizabeth W. Mata
Registration No. 38,236
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: February 21, 2008

SCHEDULE OF EXHIBITS

Exhibit A	Ownership Records
Exhibit B	Package Insert
Exhibit C	Approval Letter dated December 27, 2007
Exhibit D	U.S. Patent No. 5,218,108
Exhibit E	USPTO Maintenance Fee Record for U.S. Patent No. 5,218,108
Exhibit F	Document Indicating Commencement of Phase III Trial
Exhibit G	Chronology regarding VOLUVEN®